

How to significantly reduce the incidence of cervical cancer ?

賴瓊慧教授

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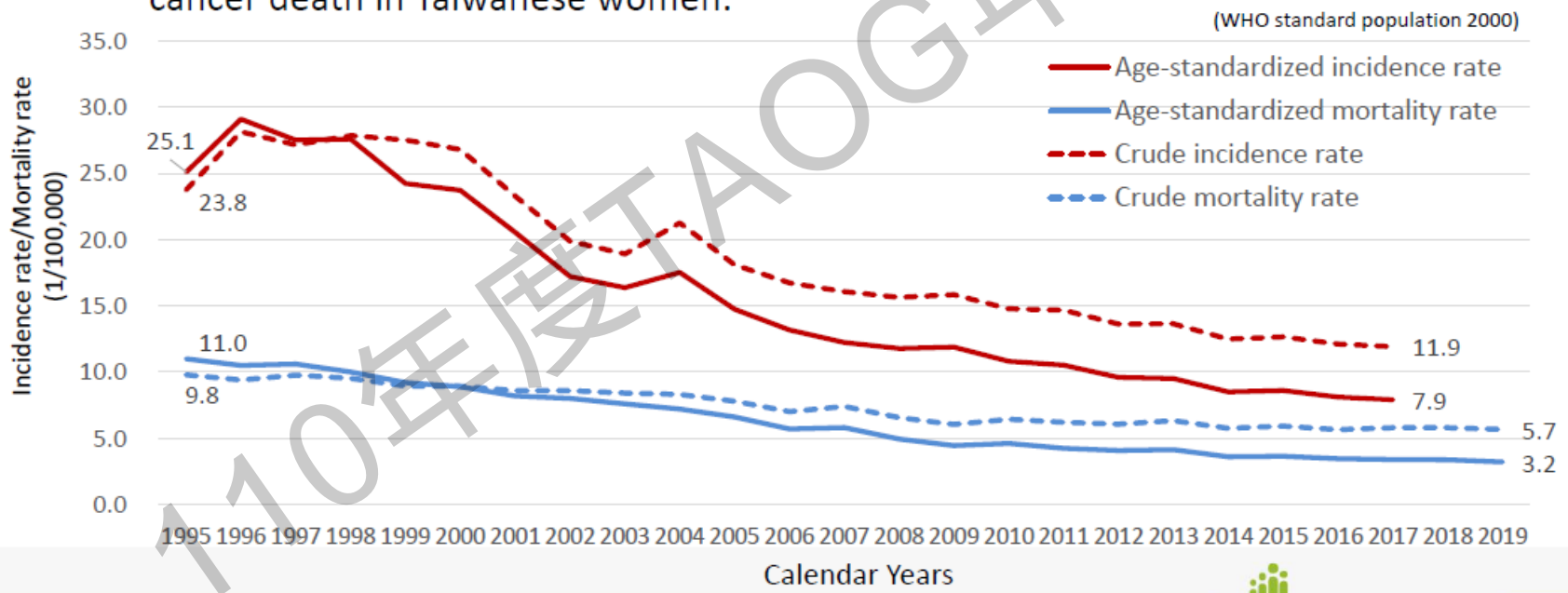
Outline

- Cervical cancer status in Taiwan
- Current cervical cancer control framework in Taiwan
- Previous population-based research in Taiwan
- HPV testing by self-collected vaginal samples is one of the solution for breakthrough of coverage rate in Taiwan
- Multi-age cohorts and gender neutral HPV vaccination policy on the promise of cervical cancer elimination
- Conclusions



Background of Cervical Cancer Prevention

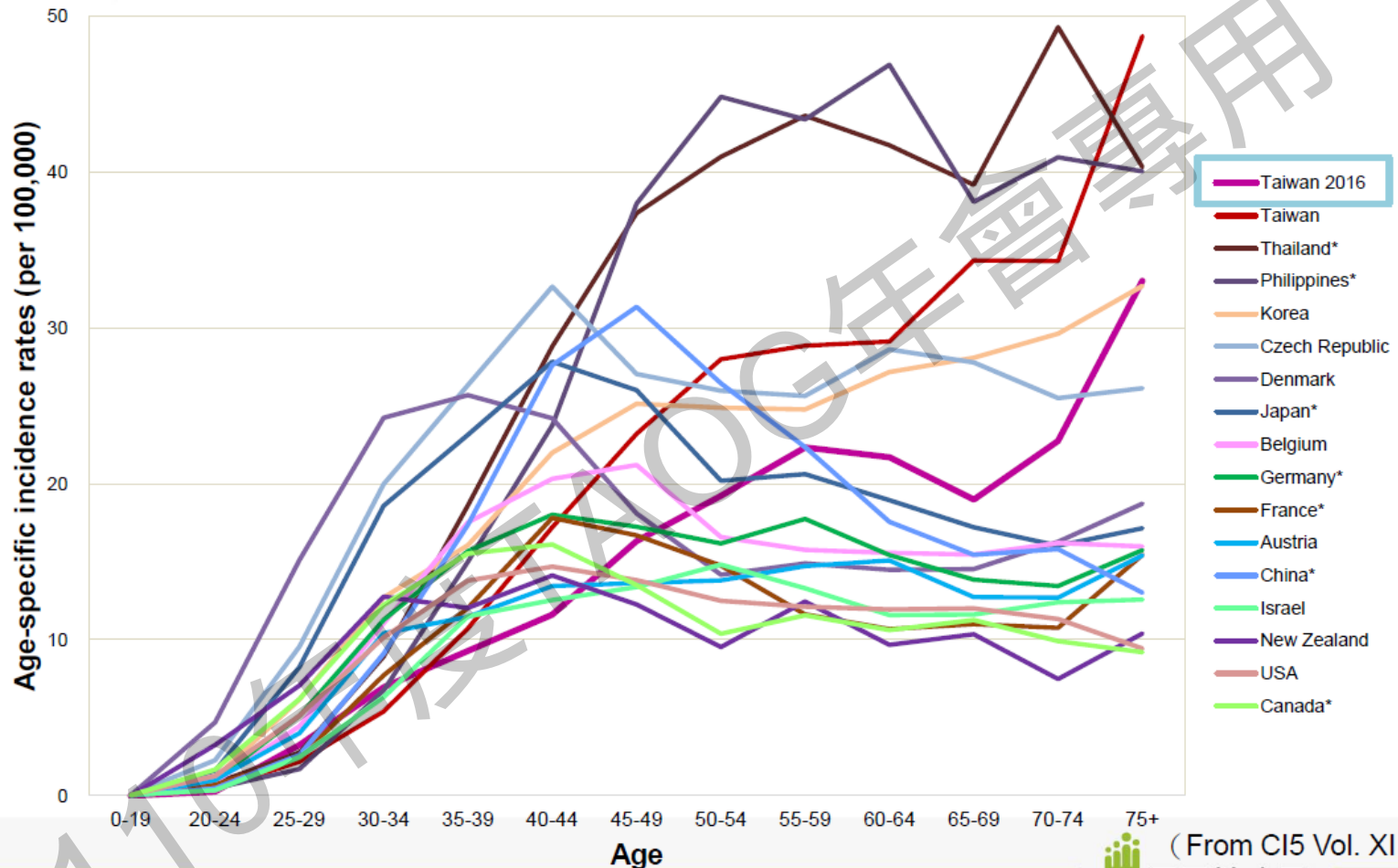
- The incidence of cervical cancer was the top of 10 causes in Taiwan in 1995. The government has promoted pap smear screening since 1995.
- The standardization rate of cervical cancer has declined from 25.1 per 100,000 people to 7.9 per 100,000 people in 2017, and the standardized death rate has dropped from 11 per 100,000 people to 3.2 per 100,000 people in 2019.
- Although the incidence of cervical cancer has declined, it is still 8th of 10 causes of cancer death in Taiwanese women.



Adapted from HPA, Taiwan



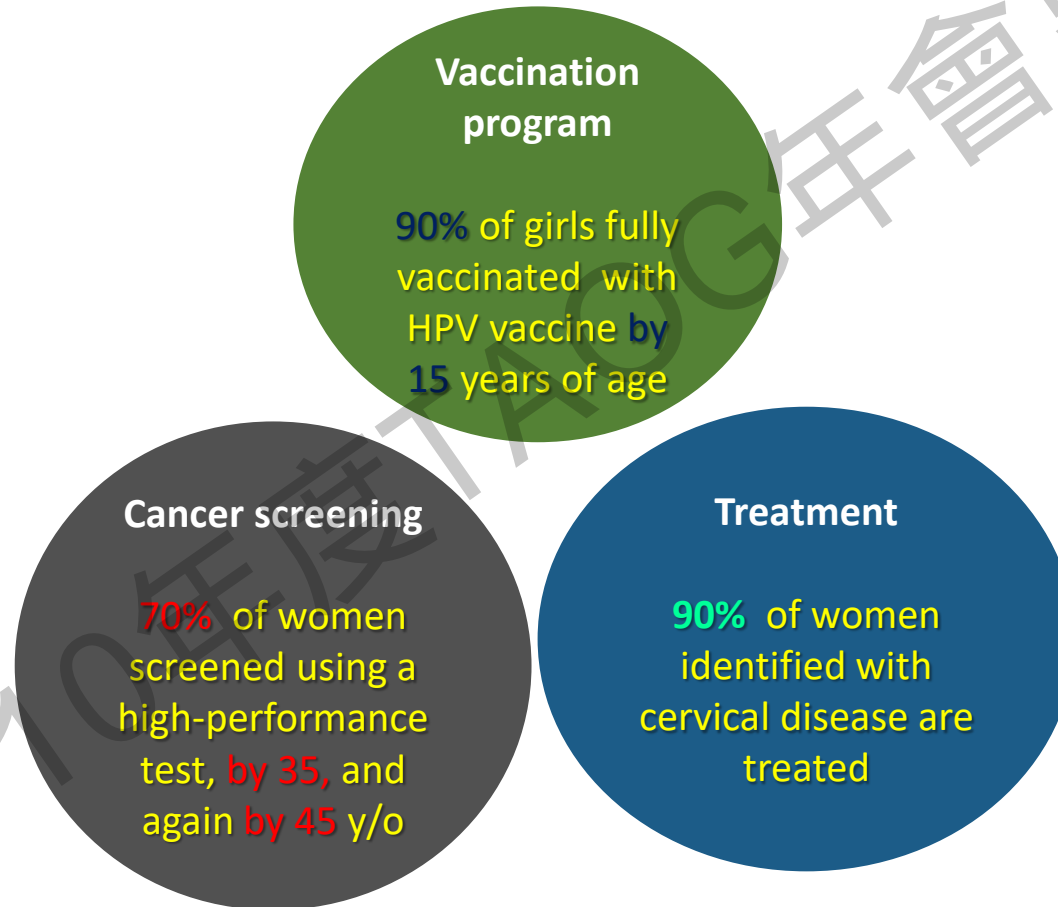
Age-specific incidence rate of cervical cancer , 2008-2012 -Country comparison-



Exit cervical cancer screening program **at 65** years old **may not be appropriate** when invasive cervical cancer incidence and mortality remains highest in these women.

Adapted from HPA, Taiwan

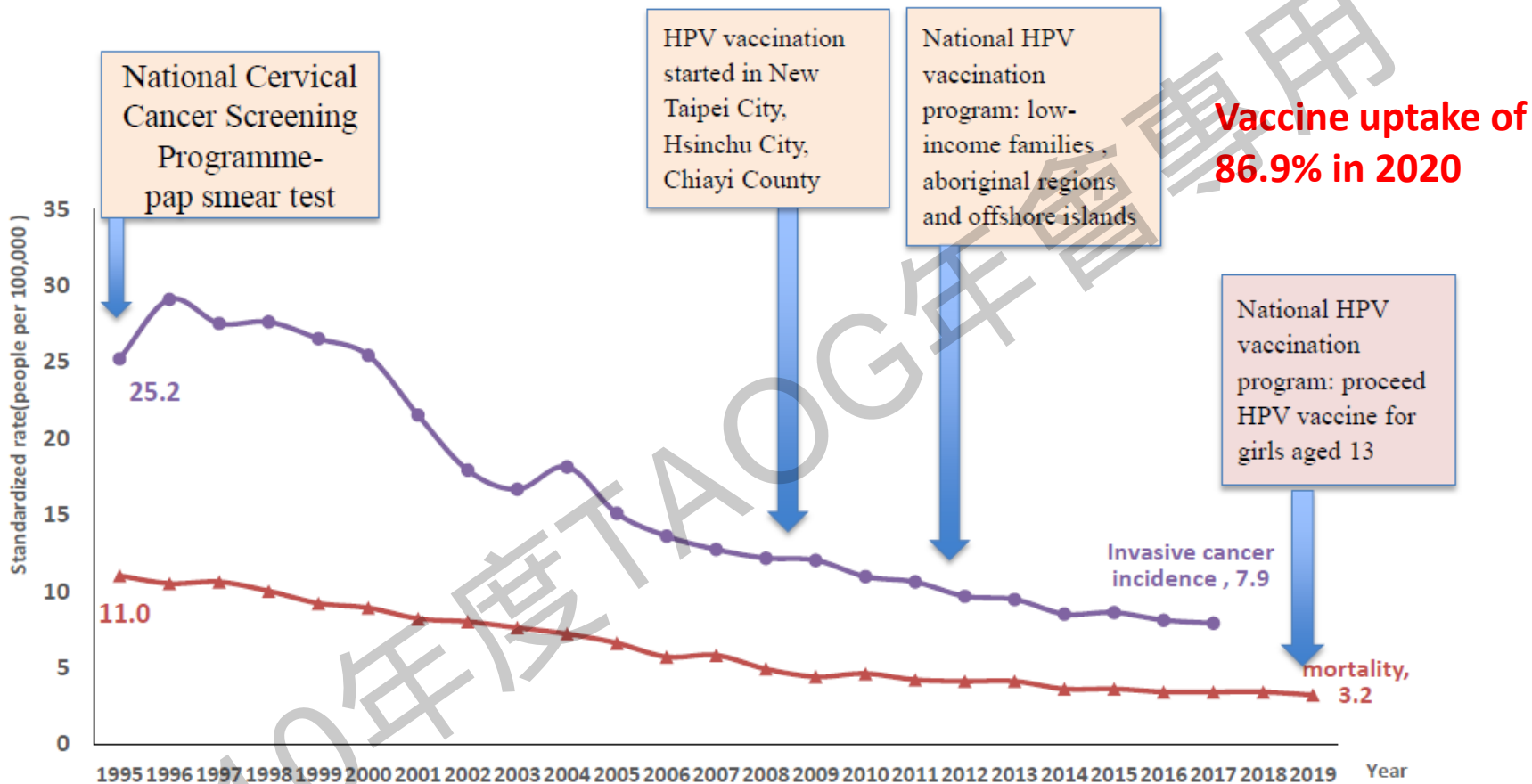
WHO: The 2030 targets towards elimination of cervical cancer meeting the following 90-70-90 targets by 2020 will put all countries on the path to elimination



Adapted from
PHA, Taiwan



Implementation of vaccination program



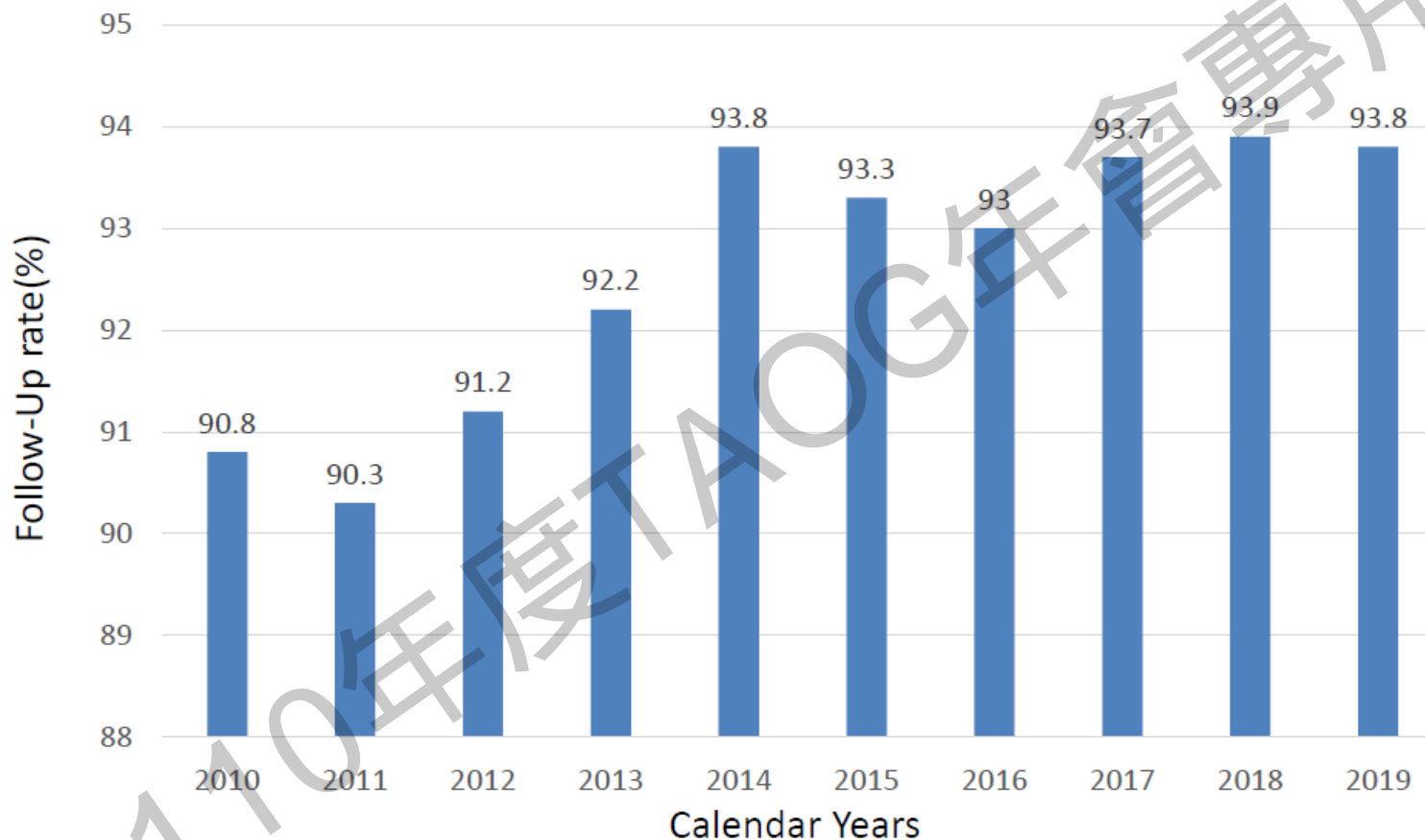
Source: Health Promotion Administration, MOHW

MK Chen et al. 2011 J Eval Clin Pract, 17, 1050-1058.
 E Suarez, CJ Chen et al, 2008 Vaccine 26S,F29-F45
 EJ Dasbach et al, 2008 Asian Pacific Cancer Prev, 9, 459-466



Adapted from HPA, Taiwan

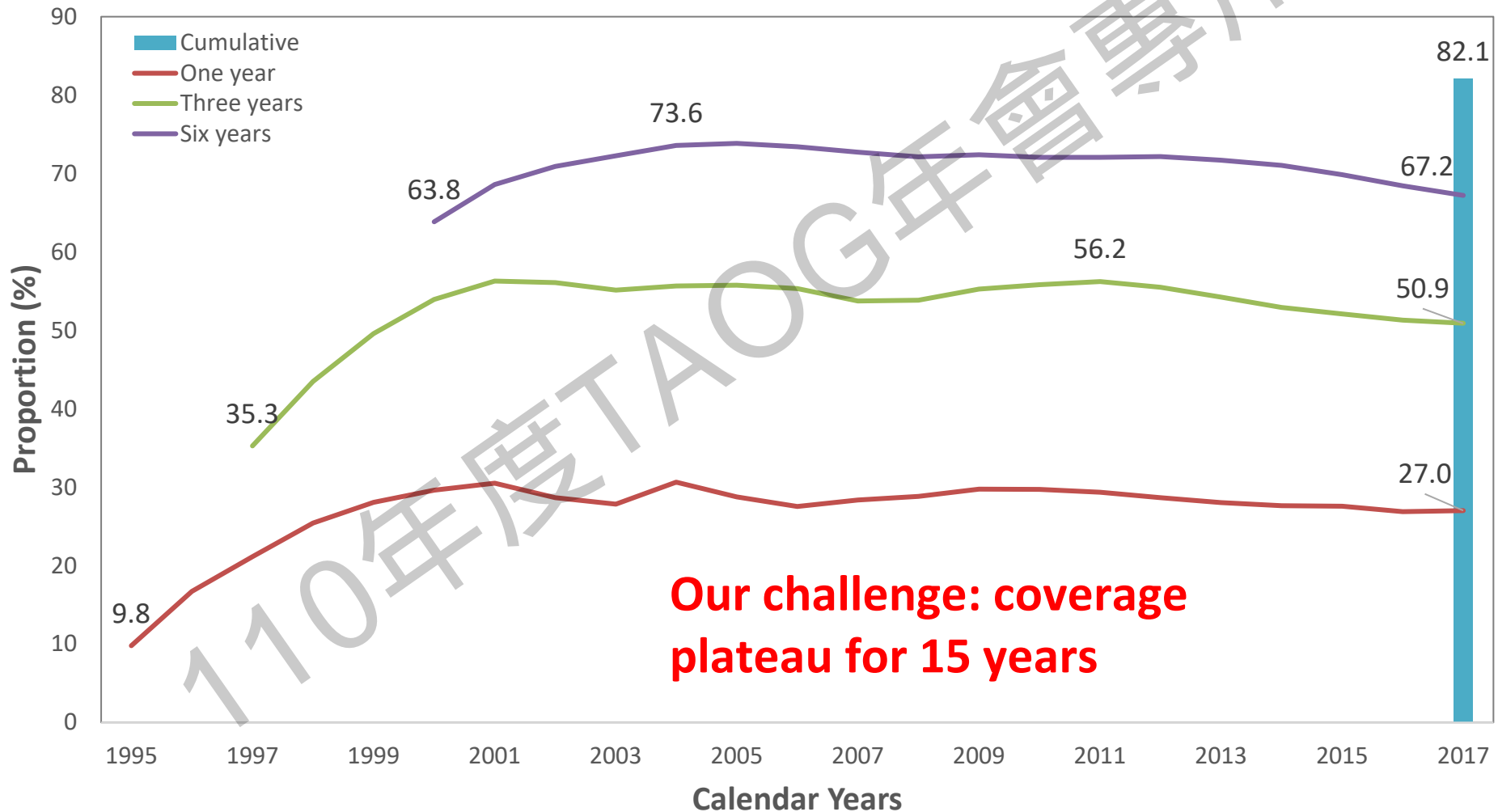
Women with Abnormal Pap smears followed to receive treatment and care



Adapted from HPA, Taiwan

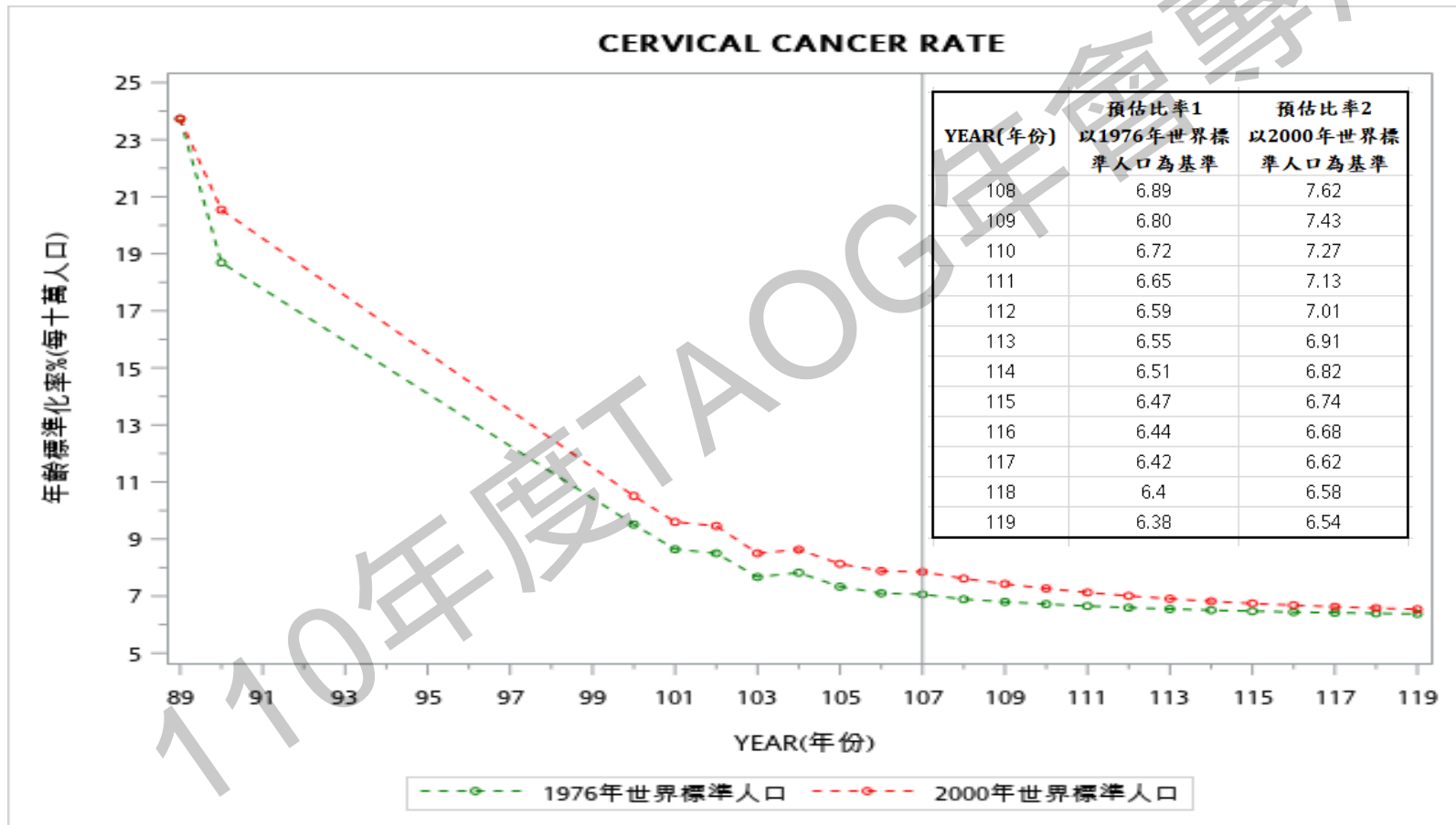


Cervical cancer screening participation rate in Chinese Taipei, 1995-2017



Adapted from HPA, Taiwan

Predicting cervical cancer 2030 in Taiwan (WHO target 4.00/100,000)



Cervical Cancer Screening Program Integrating Pap Smear and HPV DNA Testing: A Population-Based Study in Taiwan

Chao, ...Lai, et al.

Int J Cancer 2008;122:2835-2841



結果

- 2004-2005長庚醫院婦產部與桃園縣衛生局合作按人口比率到13個鄉鎮市做子宮頸抹片檢查和HPVDNA檢測共10014人次
- HPV 盛行率 **10.8 %**
- 前三名是HPV-52, -18, and -58.
- **59位**子宮頸抹片異常者最後病理証實為子宮頸皮內腫瘤中度以上(CIN 2+)，子宮頸抹片正常HPV陽性有**12位**CIN 2+，子宮頸抹片正常HPV陰性有只**2位**CIN 2+
- 子宮頸抹片偵測CIN 2+靈敏度(Sensitivity) : **81.9%**
(59/72)
- 子宮頸抹片檢查和HPV檢測CIN 2+靈敏度:**97.2%**
(70/72)



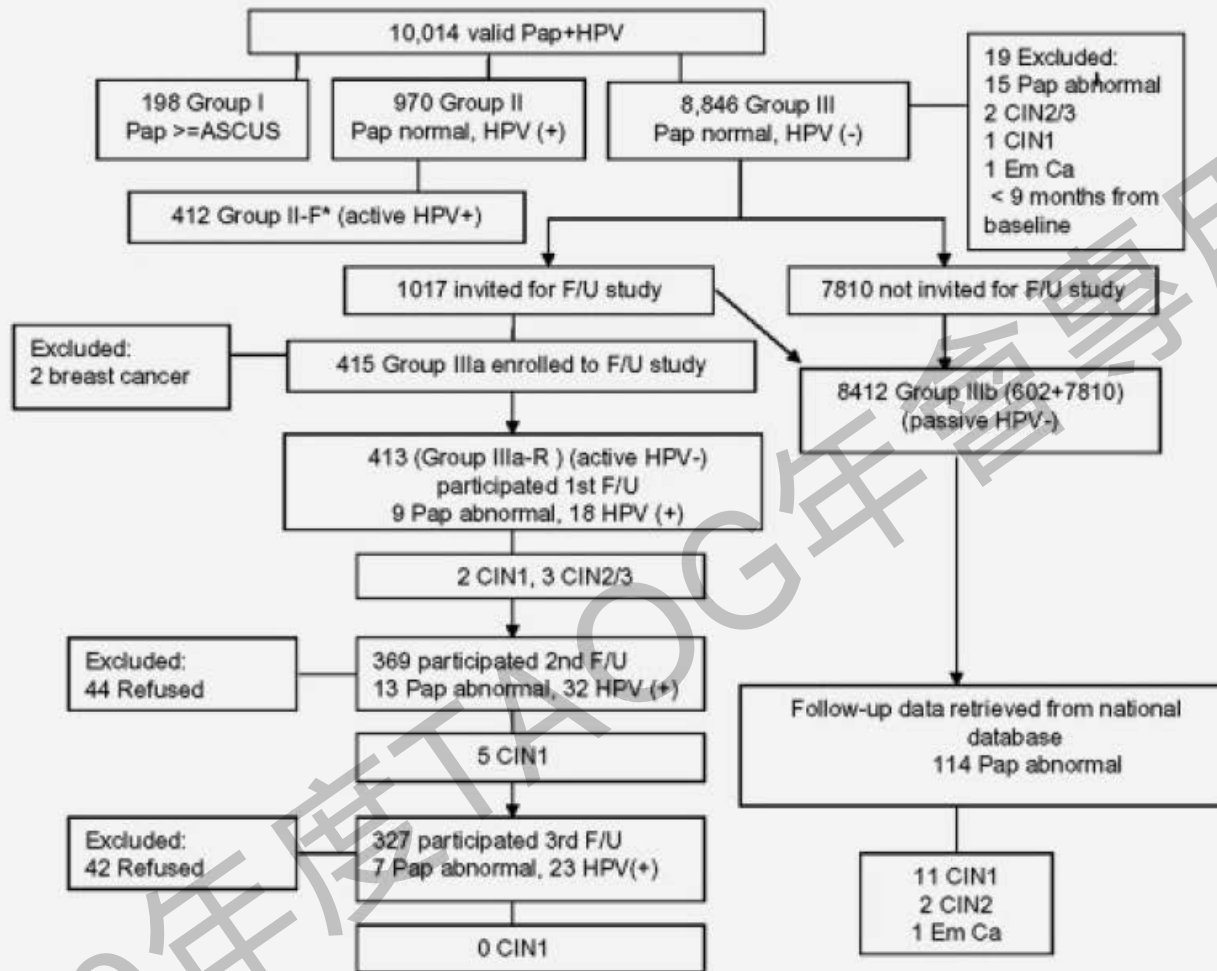


Figure 1. Flow diagram of the study. HPV indicates human papillomavirus; F/U, follow-up; CIN, cervical intraepithelial neoplasia; Em Ca, endometrial cancer. *Active HPV-positive subjects in previous study.¹¹

Angel Chao, Chee-Jen Chang, Chyong-Huey Lai*, et al.
Int J Cancer 2010;126:191-198



Results

- From the **passive follow-up normal cytology/HPV-negative group (n=8825)**, **only one** case progressed to CIN2 within 3 years probably after HPV acquisition.
- **A screening interval of 3-5 years for those with double-negative co-tests is safe and recommendable.**

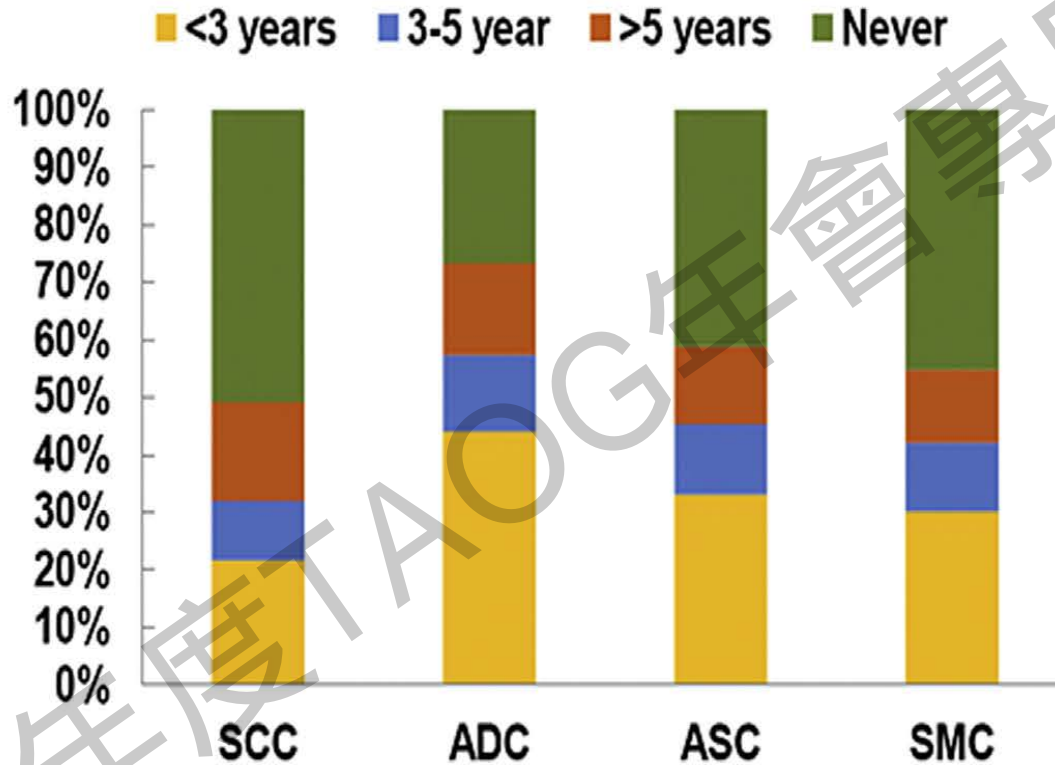


Pap smear history and behavior of patients with newly diagnosed cervical cancer in Taiwan

- 141 women with newly diagnosed cervical cancer at CGMH, Taiwan were prospectively enrolled between January 2007 and June 2008.
- Of the 141 patients, 62 (44.0%) had never had a Pap smear before diagnosis, 10 (7.1%) did not know about the Pap smear, only 30 (21%) reported having had more than three Pap smears in their lifetime.



(B)



>40% of all cervical cancer patients have never had a Pap smear.
Chiang YC, et al. Taiwan J Obstet Gynecol 2017; 56:442-8.



Pap smear history and behavior of patients with newly diagnosed cervical cancer in Taiwan

- Stepwise logistic regression identified **perceived potential pain, fear of embarrassment, and the number of sexual partners of the male consort** as independently associated with the number of previous Pap smears (*0 versus ≥ 1*).
- The need for developing more comfortable methods of cervical cancer screening is highlighted.
- **Education strategies** should be focused on improving access to never-users.



Detection of CIN with self-obtained HPV test in women without Pap smear for 5 years and analysis of attributing factors *(Chou, Huang,...Lai, et al. J Formos Med Assoc 2016; 115:1089-1096.)*

- Between Mar 2010 and Sep 2012, a total of **10,693** women who had not attend the national Pap smear program for **5 years** were invited to this study. Of them, 383 responded and 381 submitted questionnaire but only **305 (2.85%) with informed consent and HPV test samples returned.**
- Reasons of not attending screening included lack of time, embarrassment, feeling of low risk, fear of positive results and perceived potential pain.



Detection of CIN with self-obtained HPV test in women without Pap smear for 5 years and analysis of attributing factors *(Chou, Huang,...Lai, et al. J Formos Med Assoc 2016; 115:1089-1096.)*

- 47 women (**16.7%**) had a positive HPV testing, and **14** accepted further survey to find **two CIN2+**. Another two cases of CIN2+ were identified from national registry database. Cost of **direct mailing self-samplers** seemed less than that **on-request** (NT\$ 434,866 to 164,229 with response rate of **5%-15%** versus NT\$683,957 for detecting one CIN2+).
- Although studies from some of the western countries suggest that self-sampling could increase participation among **underusers**, the results of this study indicate **a different approach** must be explored to improve the coverage rate of Pap smear of the culture characteristics like Chinese Taipei.



Prospective controlled trial with national registry data-based long-term follow-up to improve coverage of cervical screening

- **There is no IVD has been approved can be use for primary cervical cancer screening using HPV testing from self-sampling vaginal specimens so in the world.**
- HPV testing by self-collected vaginal samples with reflex cytology versus Pap smear for the detection of CIN2+ : a self-controlled trial with national registry data-based long-term follow-up.
- Such study might enhance screening coverage, which can be proposed by **academia** in collaboration with **private sectors** and **government**.
- Direct mailing-in, public health nurses accessed, and a mobile sampling van will seek collaboration with **Public Health Bureau of Counties and Cities**.



Advantages and limitations of self-sampling

- More comfortable
- More convenient
- Less embarrassing
- Less painful
- **Avoid go to hospital or places with clustering of people to reduce risk of COVID-19 infection**
- Concern about test accuracy
- **No medical device has been approved for HPV primary screening using self-sampled specimens for cervical neoplasia in Taiwan**



Self-sampling for HPV testing for cervical screening

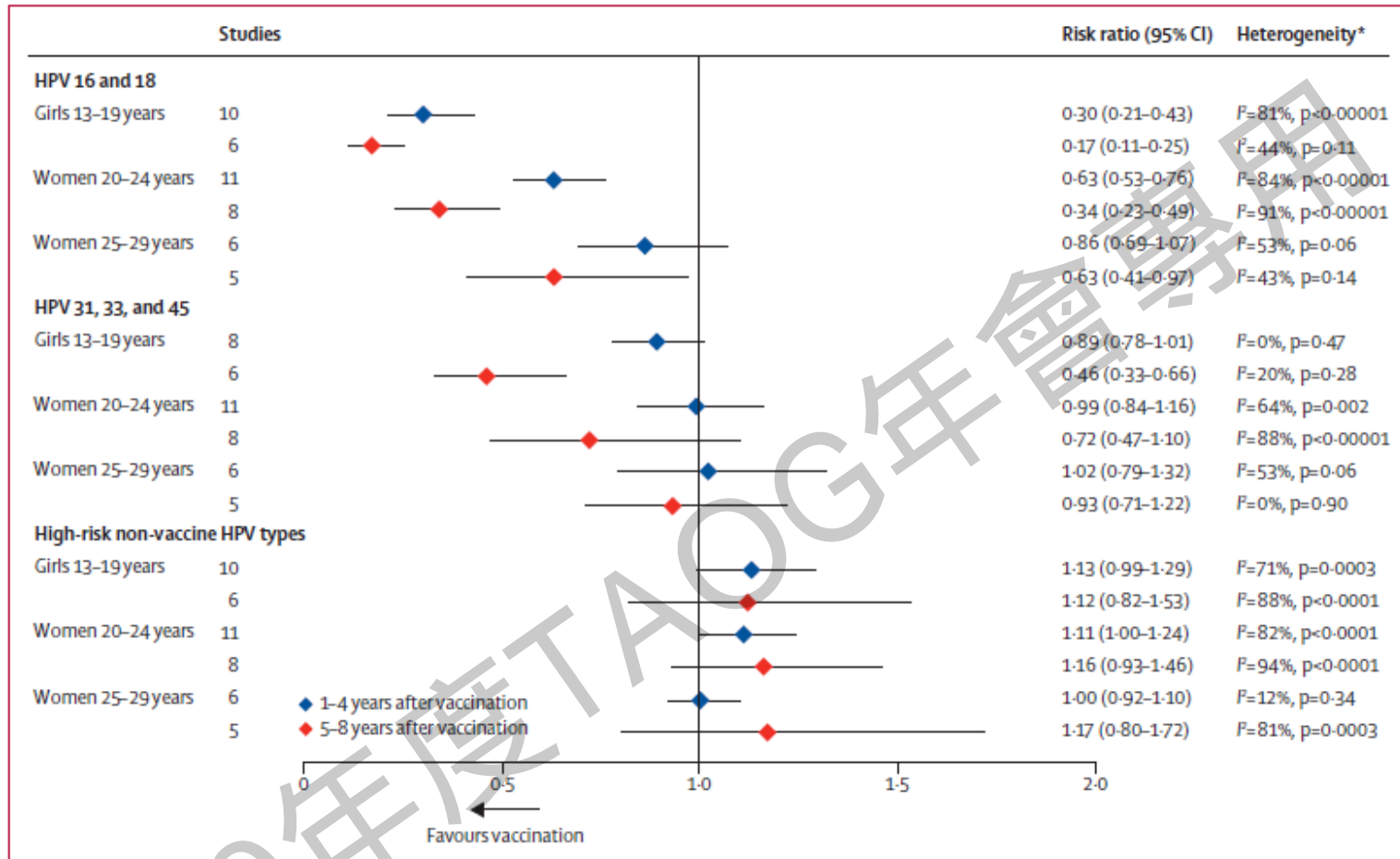
- Self-collected specimen, when tested with a PCR-based HPV assay, achieve accuracy similar to that tested on physician-collected sample
- How to facilitate willingness of participating cervical screening through self-sampling among those under-/un-screened needs to be studied.
- HPV typing for risk stratification and to define persistent infection
 - Risk stratification is an additional benefit if hrHPV typing applied for primary screening?
 - A long-term follow-up by national registry database is feasible in Taiwan



Prospective randomized trial with national registry data-based long-term follow-up to improve coverage of cervical screening

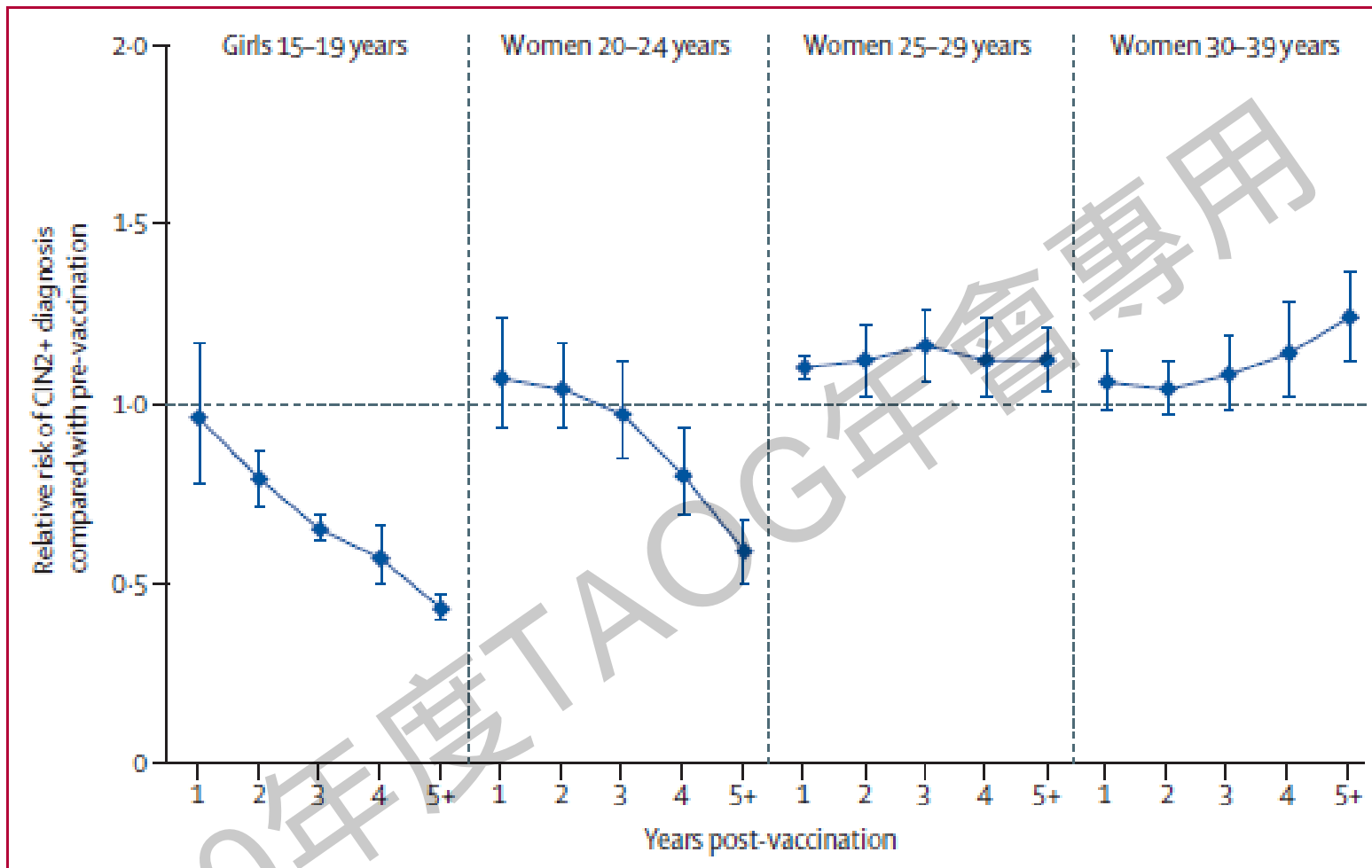
- HPV testing by self-collected versus physician-collected samples for the detection of CIN2+ among **under-users** of Pap smears: a randomized trial with national registry data-based long-term follow-up.
- Such study might enhance screening coverage, which can be proposed by **academia** in collaboration with **private sectors** and **government**.





Metaanalysis施打二/四價疫苗後HPV盛行率的變化 [Drolet et al. Lancet 2019; 394:497-509.](#)

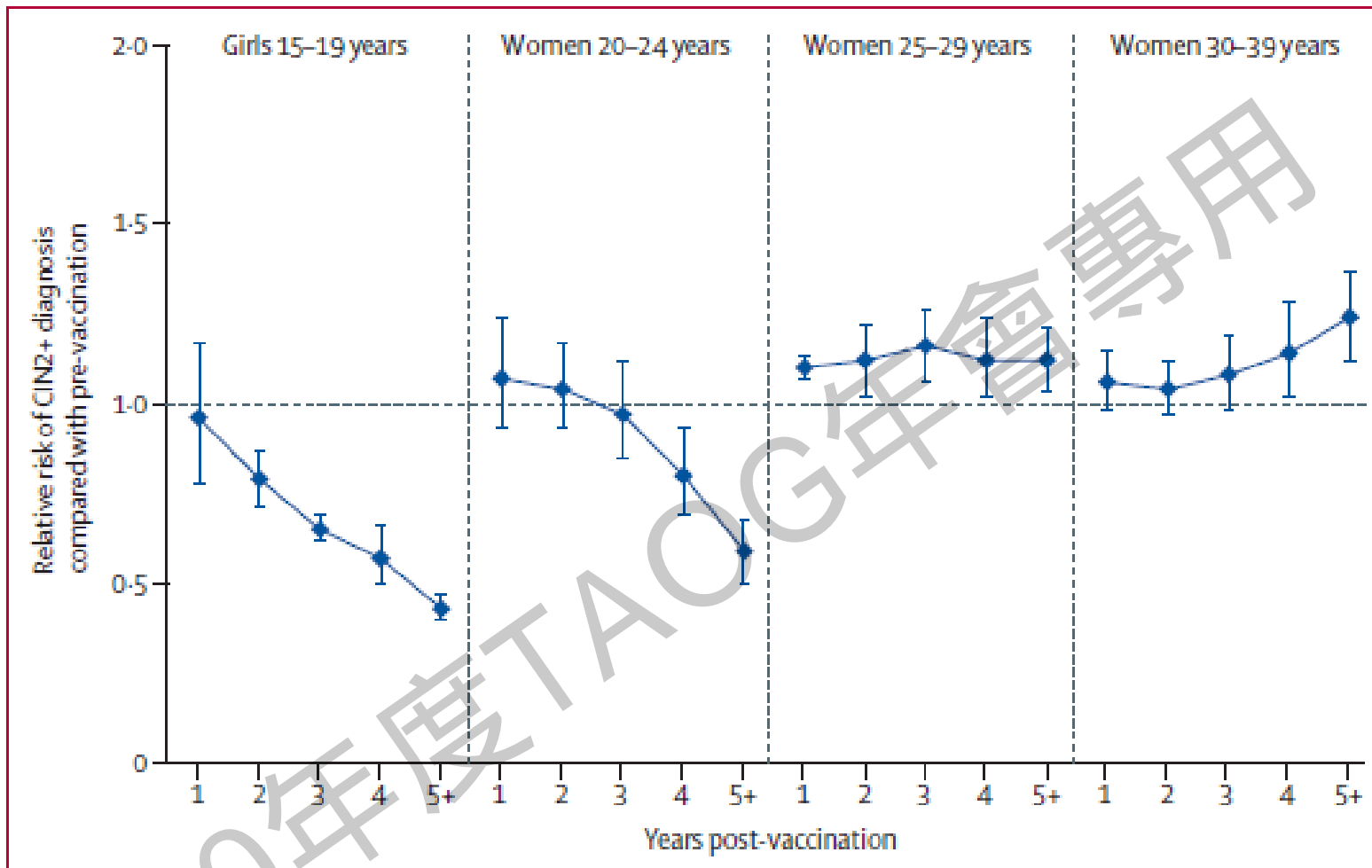




在多世代疫苗接種且高覆蓋率國家中，僅對女孩進行HPV疫苗接種後的最初7年中，接受過疫苗的**15-24歲**女孩和婦女中**CIN2+已有顯著下降**

Drolet et al. Lancet 2019; 394:497-509.





在多世代疫苗接種且高覆蓋率國家中，僅對女孩進行HPV疫苗接種後的最初7年中，接受過疫苗的**15-24歲**女孩和婦女中**CIN2+已有顯著下降**

Drolet et al. Lancet 2019; 394:497-509.



Metaanalysis施打二/四 價HPV疫苗生殖疣(菜花)

8年後

Drolet et al. Lancet 2019;
394:497-509.

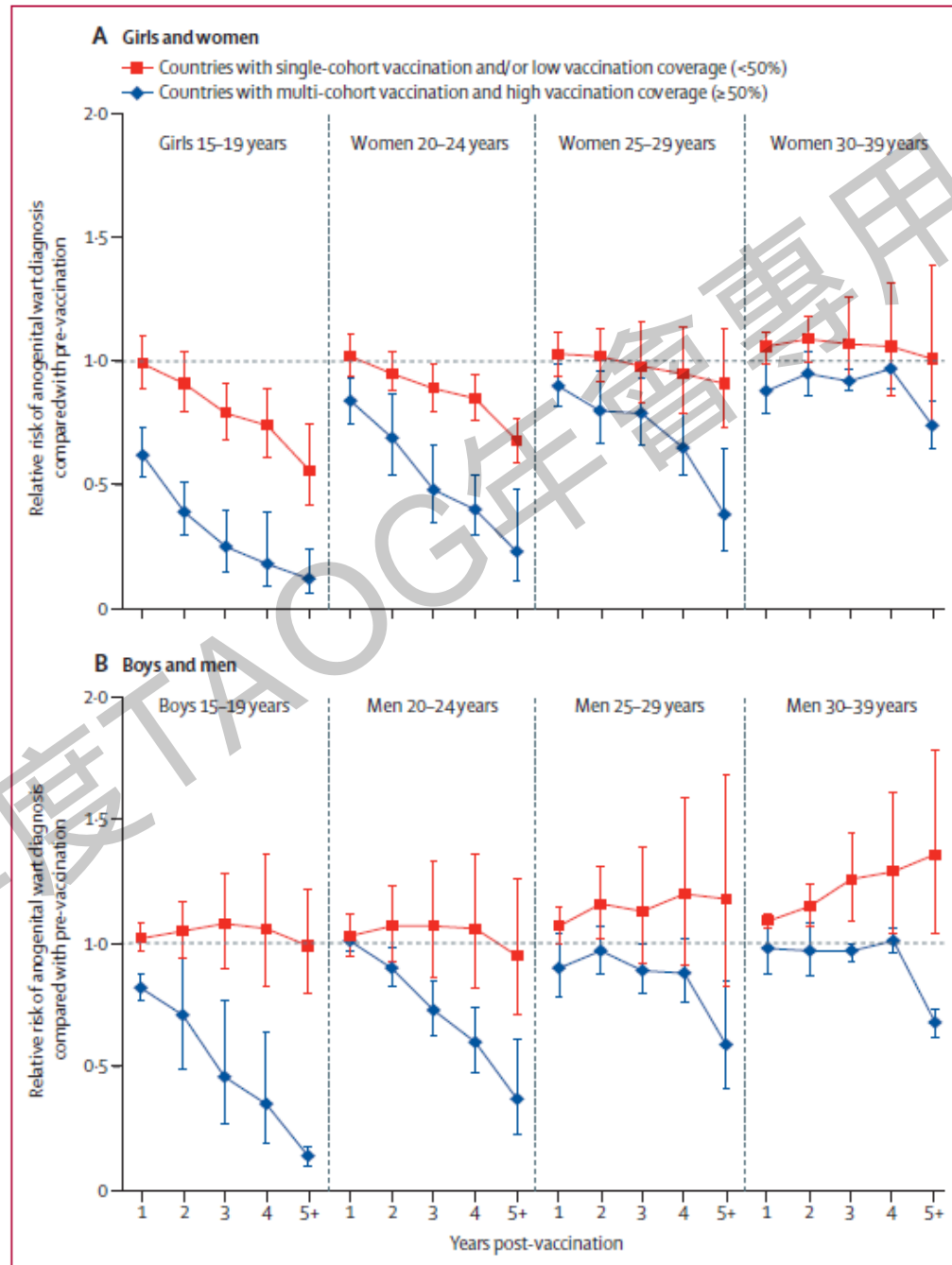
在多世代疫苗接種(藍)
15-29歲女性和男性已有顯著下降:單世代疫苗接種(紅)生殖疣(菜花)就只有15-24歲女性有下降

多世代疫苗接種且兩性皆接種國家中，

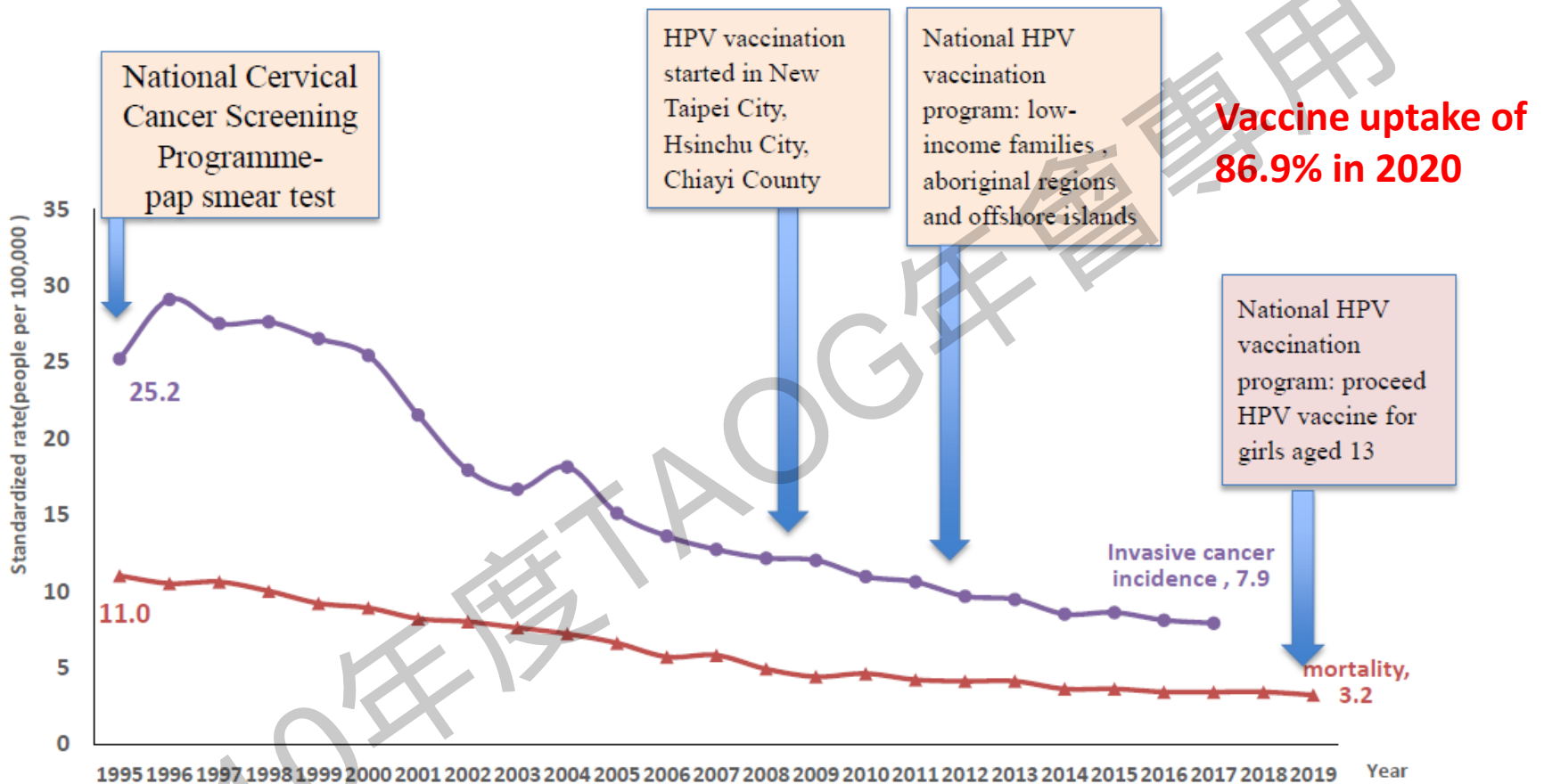
15-19歲下降**67%**

20-24歲下降**54%**

25-29歲下降**31%**



Implementation of vaccination program



Source: Health Promotion Administration, MOHW

MK Chen et al. 2011 J Eval Clin Pract, 17, 1050-1058.

E Suarez, CJ Chen et al, 2008 Vaccine 26S,F29-F45

EJ Dasbach et al, 2008 Asian Pacific J Cancer Prev, 9, 459-466



Adapted from HPA, Taiwan

HPV-related head and neck cancers

- In addition to cervical cancer, a substantial portion of head and neck cancers can be attributed to HPV, including oropharyngeal cancer (45.8%) of laryngeal cancer (22.1%), and oral cancer (24.2%) .¹
- Few data are available on the HPV-related head and neck region, a recent study showed that HPV DNA/p16+ rate was 28.4% in oropharyngeal cancer and 21.2% in oral cavity SCC in Taiwan.^{2,3}

¹Lancet Oncol 2014; 15: 1319–31. ²PLoS ONE 2021; 16(4): e0250530.

³J Clin Virol 2013; 57: 331-337.



台灣女性 10 大癌症，按發生率及死亡率排序 （以年齡標準化率^{2b}排序）

女性 10 大癌症（不含原位癌³）發生率（每 10 萬人口），民國 106 年

順位	ICD-O-3	原發部位	個案數 (人)	粗發生率	年齡標準化 發生率 ^{2a}	年齡標準化 發生率 ^{2b}
1	C50	女性乳房	13,965	117.83	73.11	78.88
2	C18-C21	結腸、直腸、乙狀結腸連結部及肛門	6,974	58.84	30.46	34.66
3	C33-C34	肺、支氣管及氣管	6,346	53.55	28.22	31.56
4	C73	甲狀腺	3,118	26.31	18.42	19.96
5	C22	肝及肝內膽管	3,425	28.90	13.86	16.17
6	C54	子宮體	2,695	22.74	14.03	15.11
7	C56, C57.0-C57.4	卵巢、輸卵管及寬韌帶	1,521	12.83	8.54	9.19
8	C44	皮膚	1,715	14.47	6.78	7.94
9	C53	子宮頸	1,418	11.96	7.10	7.88
10	C16	胃	1,399	11.80	5.86	6.76
	C00-C80	全癌症	52,387	442.02	254.30	280.96



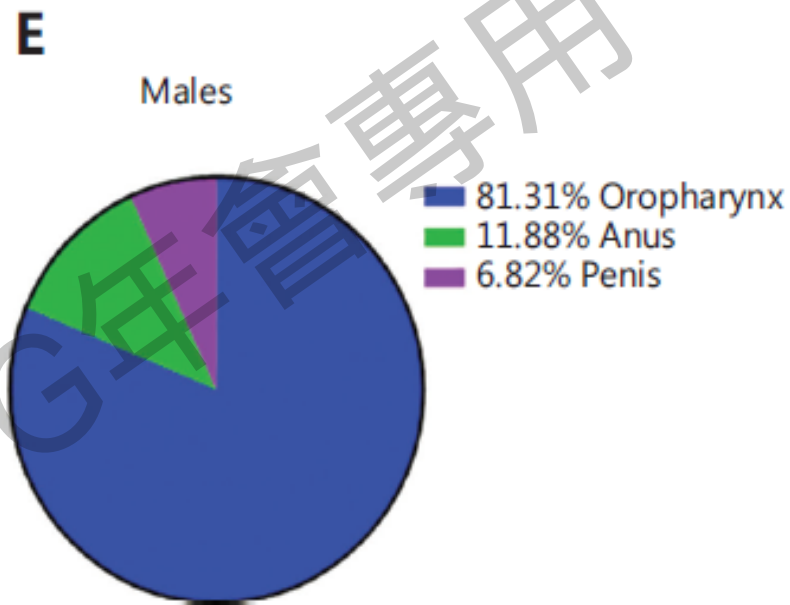
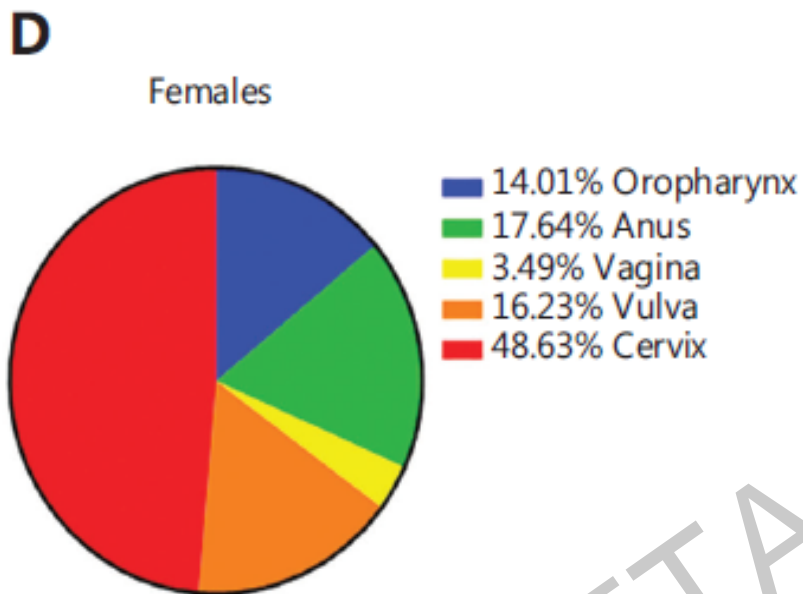
台灣男性 10 大癌症，按發生率及死亡率排序 (以年齡標準化率^{2b}排序)

男性 10 大癌症 (不含原位癌⁴) 發生率 (每 10 萬人口)，民國 106 年

順位	ICD-O-3	原發部位	個案數 (人)	粗發生率	年齡標準化 發生率 ^{2a}	年齡標準化 發生率 ^{2b}
1	C18-C21	結腸、直腸、乙狀結腸連結部及肛門	9,434	80.50	46.15	52.21
2	C22	肝及肝內膽管	7,800	66.56	39.08	43.48
3	C33-C34	肺、支氣管及氣管	7,936	67.72	37.86	43.46
4	C00-C14 ³	口腔、口咽及下咽	7,058	60.22	38.27	41.15
		口腔	4,569	38.99	24.95	26.91
		口咽	1,410	12.03	7.59	8.09
		下咽	1,079	9.21	5.73	6.15
5	C61	攝護腺(前列腺)	5,866	50.05	26.64	31.65
6	C15	食道	2,563	21.87	13.47	14.50
7	C16	胃	2,304	19.66	10.74	12.40
8	C44	皮膚	2,089	17.82	9.44	11.31
9	C67	膀胱	1,707	14.57	7.78	9.11
10	C91-C95 ⁵	白血病	1,383	11.80	8.40	8.98
	C00-C80	全癌症	59,297	505.97	299.21	335.71

2017癌症年報口咽癌的發生率(2000年年齡標準化)十萬分之 8.09 已經超過子宮頸癌的 7.88





人類乳突病毒HPV造成的癌症依性別的分佈



按性別，年代和人口群風險之口咽HPV帶原率的統合分析

Subgroup	No. of studies	Prevalence (%)	95% CI	Heterogeneity	
				I ² (%)	P value
總計	63	7.7	6.8-8.6	97.7	< 0.001
性別					
男性	28	9.3	6.4-12.5	97.1	< 0.001
女性	26	5.5		95.1	< 0.001
地區					
歐洲	21	9.9	7.2-12.5	96.2	< 0.001
北美	25	7.7	5.9-9.6	98.7	< 0.001
亞洲	3	2.6	0.6-4.6	95.3	< 0.001
非洲	5	7.0	5.3-8.6	10.4	0.347
~1999	4	3.0	0.5-5.6	91.5	< 0.001
~2009	23	8.9	7.1-10.6	97.8	< 0.001
~2017	5	7.9	6.0-9.8	97.6	< 0.001

口咽的HPV帶原率平均為**7.7%** *Tam S, et al. Oral Oncol 2018; 82:91-9.*



HPV疫苗在口腔和口咽HPV感染中的隨機對照試驗

- 芬蘭38,631在1994 -1995 出生的青少年隨參加了機對照試驗
- Arm A, 90% 男女孩都接受二價HPV疫苗; Arm B, 90% 女孩都接受HPV疫苗; Arm C,接受HBV疫苗(對照組).
- 3-6年後，女孩18.5歲時收集口咽樣本進行HPV檢測
- 疫苗效度: HPV 盛行率 in Arm A+B vs Arm C:
HPV16/18盛行率降低**82.4%**, HPV31/45降低**75.3%**,
HPV31/33/45降低**69.9%**.

Lehtinen M, et al. Int J Cancer 2020; 147:170-4.



性別中性的HPV疫苗接種策略-男性HPV疫苗的接種

- 減少生殖疣有證據、陰莖癌及肛門癌及其癌前病變可預期
- 減少口咽癌(oropharyngeal cancer)大致上臨床試驗目標只有減少HPV感染，有限的間接證據
- HPV疫苗對男性的影響，醫界的觀念、民眾的知識與了解有限，都需要加強宣導



結論

- 把 HPV 檢測納入子宮頸篩檢的系統，並利用自我採樣的HPV檢測來增強篩檢覆蓋率
- 多年齡世代HPV疫苗接種策略：補打16-18歲女孩的疫苗。鼓勵在19-25歲的女性中進行自費HPV疫苗接種和產後HPV疫苗接種
- 性別中性(Gender neutral)的HPV疫苗接種策略，有待醫療服務提供者及民眾對這個議題有更好的認識，並且衛生主管機關透過各種管道與和公眾進行溝通





15:11

婦癌研
起人暨

ISKEA-IDS
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Thank You